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TYPES OF INSULIN DELIVERY DEVICES

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Abstract: Diabetes mellitus is a big issue on the human society that covers a lot of people in the world wide. Many patients are suffering from T2DM (Type 2 Diabetes Mellitus) and all patients who are suffering from the (T1DM) (Type 1 Diabetes Mellitus) requires the administration of insulin to maintain the blood glucose levels. There are a number of methods to subcutaneously deliver the insulin such as insulin pen, insulin pump, jet injector, transdermal patches and inhaled insulin. Inhaled insulin delivery method was first approved noninvasively. This review article focuses on the types of insulin delivery devices and on different possible types of insulin delivery devices.

Index Terms - Types of insulin delivery system, Jet injector, Insulin pen, Transdermal patches and Inhaled insulin.

I. Introduction: In humans, porcine insulin is present. Insulin is responsible for controlling the energy metabolism with the help of epinephrine. While being stored in cytosol, insulin is released by the process of exocytosis. The Metabolism of insulin takes place by enzyme known as Insulinas. (Verma et al., 2014) The International Diabetes Federation estimated 366 million people had diabetes in 2011 and it will rise to 552 million by 2030 (Shah et al., 2016). For the Patients who are suffering from hyperglycemia, insulin is useful to overcome the hyperglycemia. In earlier insulin was given orally to control hyperglycemia (Marcus, 2008). In 2007 DM patients covered around 12 million of count in which most were 60 years of age or older. It is almost one-half of the DM population and this will increase in 2020 around 16 %. (Mohanty and Das, 2017) In USA around 21 million people out of 7% of the population have diabetes. American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) and American College of Endocrinology/American Association of Clinical Endocrinologists (ACE/AACE) have issued the guidelines on maintaining the blood sugar levels. In 2008 according To ADA insulin therapy is provided to those patients whose glycosylated hemoglobin (HbA_{1c}) levels reach > 8.5%. Target HbA_{1c} recommendations by the AACE and ADA are ≤ 6.5% and < 7%, respectively; however the ADA recommends levels < 6% in individuals who are not experiencing hypoglycemia. (Marcus, 2008) (Wright et al., 2010) There are two types of diabetes mellitus one is TYPE 1 DM and second one is TYPE 2 DM. In treatment of type 2 DM (T2DM), multi drug regimen and insulin are required to overcome the glycemic control. (Wright et al., 2010) (Mohanty and Das, 2017)

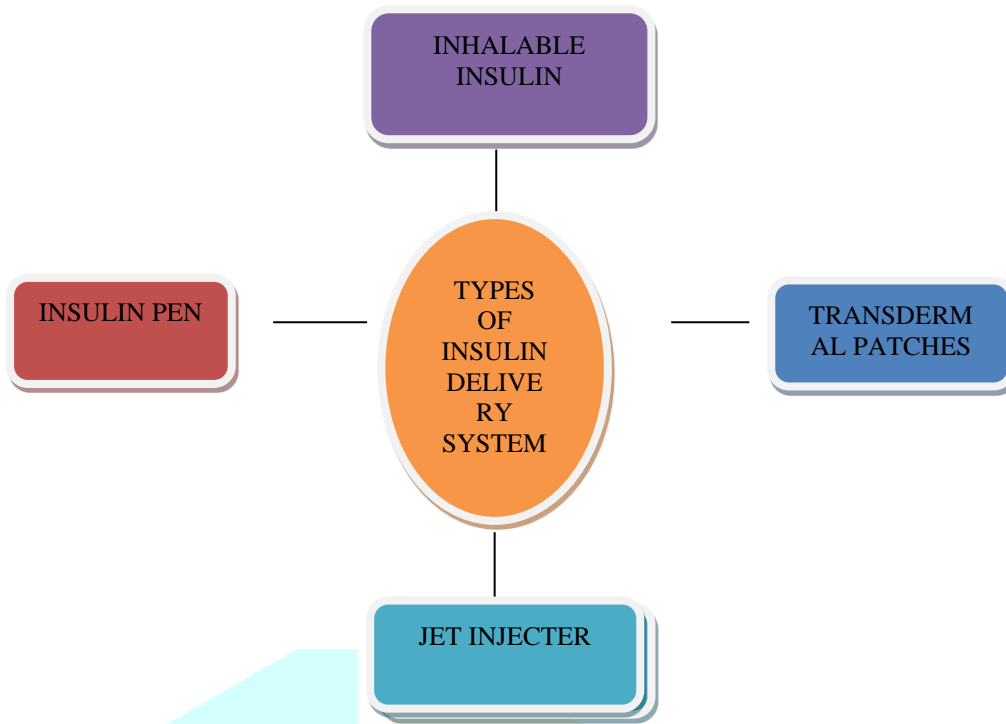
II. TYPES OF INSULIN DELIVERY SYSTEM

1. JET INJECTOR

Jet injector was used 75 years ago to vaccinate millions of people who required to be immunized. As a strategic tool, it does not gives the full potential to deliver medication through the skin. Old jet injectors are of low quality and causes infection, pain during administration and accidental injury of the operator's finger. Nowadays new design is introduced to overcome these type of problems by introducing the skin-site properties and thickness. Now jet injectors are defined as NFII and it is a Needle free drug delivery method this is high speed stream and in this drug delivers excluding vaccines and insulin. It has 1% lidocaine which provides the analgesic effect and pain score is 3 (Barolet and Benohanian, 2018). For the production of macroscopic jets, commercial jet injector was preferred. A needle-free spring action jet injection system known as Vitajet 3 is specially designed for insulin administration. (Arora et al., 2007) There is a recommendation of ADA which states that they "should not be viewed as a routine option for use in patients with diabetes" (Marcus, 2008). In this fluid contains a corticosteroid, an anesthetic agent, 5-aminolevulinic acid (ALA), onabotulinum toxin A (BoNT-ONA), bleomycin and other injectable substances. (Barolet and Benohanian, 2018).

I. There are two types of NFII injectors: (Barolet and Benohanian, 2018).

1. Spring-loaded jet injector: It follows the principle of spring mechanism and recoil. Spring is released by hitting trigger to deliver a drug.
2. Gas-powered jet injector: It consists of a gas cartridge which is with the gun through a tubing system which gives a power to piston for delivers the drug.



2. INHALABLE INSULIN

Inhalable Insulin/Inhaled Insulin is insulin which is present in the form of powder and with the help of an inhaler it is administered to the lungs. (Mohanty and Das, 2017) The products that are inhalable can be characterized into 2 types: 1) Dry Powder 2) Solution. Both the forms can be administered through different types of inhalers. (Azad et al., 2013) Absorption of inhaled insulin on the mucosal layer of the skin is high (Verma et al., 2014) Exubera was the first inhaled insulin which was developed by Pfizer pharmaceuticals named as PfizerD (dose 1mg to 3mg) (Shah et al., 2016). This was the first inhaled insulin marketed product in 2006, but unfortunately because of its poor sale at market level, it was not renowned and was withdrawn in the year of 2007. Nowadays, Mankind produced Afrezza inhaled insulin and this was developed by the use of different technology such as technosphere and this was approved by FDA (food and drug administration) in 2014. (Mohanty and Das, 2017) Afrezza inhaled insulin has an onset of action of about 15 minutes and 2-3 hours in duration which is attained after a meal to control blood glucose levels (Shah et al., 2016). Exubera is produced from the ribosomal DNA and it is used for the children who are above 6 years and adult patients. (Verma et al., 2014) Second inhaled insulin was developed by the AERx insulin Diabetes Management System (AERxiDMS; Aradigm Corporation; Hayward, California/Novo Nordisk) but unfortunately this was discontinued because of its least safety as compared to other ones. (Marcus, 2008)

3. TRANSDERMAL PATCHES

Transdermal patches insulin delivery is used for patients who are afraid of the needle and injection. Transdermal administration is a convenient route for insulin delivery (Shah et al., 2016). The skin consists of three layers: Epidermis, Stratum Corneum, and Dermis. The stratum corneum consists of non-nucleated protein-enriched corneocytes and intracellular domains which are lipid-enriched. The epidermis is multilayered consists basal layer, the spinous layer and granular layer and dermis is the most inner layer. Keratinocytes and Langerhans cells are present in the epidermis which is skin immune system: fibroblasts, dendritic cells, and mast cells in the dermis. T- and B-lymphocytes in the skin-draining lymph nodes. The transdermal permeation of insulin consists of in-vitro and in-vivo. (Matteucci et al., 2015). Mechanism of skin penetration enhancer are as follows:

- 1) Increased drug solubility
- 2) Optimization of the formulation
- 3) Increased diffusion coefficient (apply shortly in time and high voltage pulses)
- 4) Provision of additional driving force (small electric currents techniques) (Matteucci et al., 2015) (Shah et al., 2016).

Recombinant human hyaluronidase (rHuPH20) is used to increase the absorption of insulin from subcutaneous tissues. Transdermal patches are used to treat skin injury; burn and discomfort. (Shah et al., 2016) Characterization of transdermal insulin are as follows:

- 1) Passive delivery
- 2) Patch, cream and spray forms
- 3) Diffusion through skin to have systemic effect. (Verma et al., 2014)

Rather than application of 1st generation transdermal patch, a gel, metered liquid spray or other topical formulation is applied to the skin which is capable of driving lipophilic drugs which are small in size directly into the stratum corneum. (Prausnitz et al., 2004)

PARAMETERS	PROPERTIES
Dose	Less than 20mg/day
Half life	< 10 hrs
Molecular weight	<400 Dalton
Melting point	<200°C
Skin Reaction	Non irritating and non-sensitizing

4. INSULIN PEN

Insulin pen was first introduced in 1970s and first insulin manufactured in 1985 that is Nova Pen (Novo Nordisk)(*Krzywon et al., 2010*)(*Selam, 2010*). The refinements are followed by various other pharmaceutical companies over the last past 30 years. Another pen device (HumaPen® Memoir™) is built-in recording last 16 injection include also time and date. Nowadays, NovoPen Echo® is designed to provide less pain because pen needles are developed in the form of shorter and thinner form and also with the Bluetooth technology with size upto (31-32 G × 5 mm)(*Kreugel et al., 2011*)(*Shah et al., 2016*). About \$174 billion was the estimated total cost of diabetes in USA in 2007.(*Davis et al., 2013*) In Europe around 80% of these pens are used and in USA only 15% are used.(*Marcus, 2008*)(*Shah et al., 2016*). According to Graff and colleagues 90% rated the *Novo Fine 30* needle as practically pain free.(*Marcus, 2008*). This also help in the treatment of diabetes mellitus patients. Many patients also found that this a reliable method to take insulin.(*Wright et al., 2010*). Pens are used by children with type 1 diabetes and that requires less amount of insulin doses(<5U)(*Selam, 2010*). Pen devices are very easy to handle and grip. Finally, it provides the less pain and takes the patient in confidence for use.(*Selam, 2010*).

III.CONCLUSION

Apart from oral and parenteral dosing of insulin, research has helped us to gain our knowledge regarding different insulin delivery systems that might be or might not be painful. Different types of insulin delivery systems have varied potency and mechanism of action when compared to each other. Insulin is a lifesaving drug/hormone for the patients suffering from DM. Insulin delivery systems such as Jet injector, Inhalable insulin, Transdermal Patches and Insulin pen are a potent and appropriate delivery systems for the administration of insulin and in future, we hope to enhance our knowledge about other possible insulin delivery systems.

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